The Fight Against Aging and Death (manifesto)

"The problem that I remain the most passionate about is for us to make some real and continued progress in the fight against aging and death. This is not just about my facing the problem, but everybody on this planet faces it, there's about 100,000 people a day who die, mostly from diseases linked to old age. And so what I always find extraordinary is how little we're doing about this. It seems that people are either in a mode of denial or acceptance, which are in some ways opposite extremes, but they both have the effect of stopping you from doing anything. If you are in denial and say this is not a problem or if you accept it and say there is nothing you can do about it, both of these are sort of passive modes and I think what we need is a much more active mode. Instead of being in denial and acceptance I'd like us to spend a lot more time fighting death. People always say that death is natural, to which I believe the response has to be there is nothing more natural than to fight death."

—Peter Thiel

"Death is impossible for us to fathom: it is so immense, so frightening, that we will do almost anything to avoid thinking about it. Society is organized to make death invisible, to keep it several steps removed. That distance may seem necessary for our comfort, but it comes with a terrible price: the illusion of limitless time, and a consequent lack of seriousness about daily life. We are running away from the one reality that faces us all."

—Robert Greene, *The 33 Strategies of War*

Introduction

If you are like most people, you have often wondered what you can do today to ensure that you live as long, and productive, a life as possible.

Death may be inevitable, even necessary from a species perspective, but our natural human instinct is of course to fight it—to make it as distant a reality as we can. And like any fight, it requires a strategy. Despite what we have all been told, the key to long life isn't as simple as drinking red wine or eating more vegetables and antioxidants (though those things probably won't hurt). I prefer a more realistic—and ideally as evidenced-based as possible—strategy, one that involves identifying the things that are most likely to cause your death and taking reasonable steps to eliminate them.

Allow me to explain.

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As we all know, there are many threats to your immediate health. Anyone can step outside their house and get hit by a bus. You could inadvertently eat something toxic or have a fatal reaction to shellfish. You could be the victim of a homicide. Or you could be the one person in all of North America who is killed by a black bear roughly every two years.

But barring any freak events, and assuming that you're not a smoker or someone who engages in ultra-risky behaviors like base-jumping and motorcycle racing on the Isle of Man, the odds that you will die as a result of a chronic disease are enormous. **In fact, if you're reading this, the odds that you will die from one of four chronic diseases that share the same underlying metabolic derangement are *at least 4 in 5!***

Think about that for a moment. Four diseases. Which are all related.

So if your goal is to live as long as possible—to maximize your lifespan—wouldn't you stand the greatest chance of achieving this by actively reducing the risk you face from these Four Horsemen of diseases (which we'll get into later)?

On Wall Street, there is a name for an investment strategy that delivers returns greater than the market. It is known as achieving alpha. I propose that with the right strategy—one that requires some unorthodox but very reasonable lifestyle choices—you can materially minimize the most realistic threats to your longevity and achieve your own personal state of alpha.

Now let's talk about how.

Hack Into Your Lifespan

In any quest to understand an aspect of human biology—in this case, anti-aging—it helps to take a look around the Animal Kingdom. Consider, for example, how lifespans differ among different species—from the tiny bacterium whose lifecycle is measured in minutes, to mosquitos (days), mice (months), birds (years), humans (decades), turtles/tortoises (perhaps centuries), and even to bristlecone pine (millennia).

Clearly, lifespan is an evolved feature of biology that varies from species to species and is encoded in that species' genome. As for humans, it looks like our 'natural' longevity is probably between 68 and 78 years. While the mean life expectancy of hunter-gatherer tribes observed throughout the 1900s ranged from only 27 to 42 years, those that reached age 45 often had two decades of life remaining—not too dissimilar from modern man.

In 1850, the life expectancy in England was only 41 years, largely due to high child and infant mortality rates and frequent exposure to pathogens in large cities, which had poor sanitation. Since the mid-1800s, however, average life expectancy has continuously increased by about 2.5 years per decade in what one author described as the "the most remarkable regularity of mass endeavor ever observed." Except for those made very recently, all previous estimates of the

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maximum average life expectancy have been surpassed—for example, Louis Dublin's (the legendary statistician and actuary of MetLife Insurance Company in the early 20th century) 1928 estimate that life expectancy would stall at 64.75 was surpassed by the 1940s. And while some argue that improvements in life expectancy are bound to slow in the near future (e.g., improvements in mortality specifically in the United States have stagnated over the past two decades) others argue this trend of approximately 3-month increases in life expectancy for each calendar year will continue for the foreseeable future.

Should the increases in lifespan over the last 100 years be attributed to 'life extension' or instead to 'death avoidance,' and as such are we only now beginning to really push the boundary of what's (im)possible in this space of anti-aging?

For starters we know that we can reliably get many species to live longer under controlled conditions than in the wild when we manipulate various parameters. By housing animals in zoos and laboratories, we remove threats from predators and other extrinsic sources of mortality. By tinkering with the animal's food—both total calories and the types of calories—we can increase their longevity.

What now for humans? What can we change about ourselves to live long and live well?

Genetic advances or big biotech breakthroughs aside, what can we do *today* to stack the odds in our favor? Can this system—our lifespan and life quality—be 'hacked,' so to speak?

The framework is simple, at least in concept. There are really two issues to be addressed—a 'defensive' issue and an 'offensive' issue—how to *delay dying* and how to *optimize living,* respectively.

Before launching into this discussion one point cannot be stated clearly—or often—enough as it's easy to lose sight of it. We should never confuse the macro optimization problem: are we optimizing to **live longer** (i.e., years of life) or **live 'better'** (define 'better' however you wish—happier, healthier, more productive, constantly stimulated, constantly at peace—there is, obviously, no right answer)? To what extent are we optimizing 'health span' or 'life span'?

As a thought experiment, if a genie popped out of a bottle and told me I could live—in perfect health—until I was 150 years old, but I would need to live in isolation from all humans, including my family, in a dark room, I would not consider it for a moment. I'd rather die at half that age, even in illness, but know that I could enjoy the company of my family and friends for another 34 years.

A less dramatic example in my own life is my behavior with respect to exercise. To this day, though my livelihood does not depend on it, I still exercise at a level and intensity that is geared toward producing the best performance in races that I am genetically capable of producing. But I am nearly convinced by the evidence in front of me that I'm 'burning too many matches' at the intensity I train and compete. In fact, I suspect I'm *increasing* my risk of cardiac disease through my activity, which we'll get into below. Furthermore, the time I invest in such exercise could be

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used to achieve happiness (or 'success') in other areas of my life—more time with my family, learning a new language, volunteering at a local soup kitchen. So just as financial decisions always require a trade-off—an opportunity cost—so too do decisions of time allocation in the pursuit of health and happiness.

So why do I exercise like a maniac wannabe pro?

Although I do think I will change in a few years, for now, I am getting more pleasure from this level of competition than I am willing to give up, despite the risk. Maybe I'm playing chicken with my own biology. It's quite possible, and perhaps we all do this in some aspect of our lives.

And for all my expertise in diet and nutrition, I also make trade-offs in that department. I am confident I know which diet is most likely to increase lifespan (more below), but I'm simply not willing to follow it entirely, at least, not yet. So I choose to do something that gives me 80% of the *long term* benefit, but still allows me about 50 to 60% of the *short term* pleasure I could theoretically have by eating anything I want. Neither right, nor wrong, just my personal choice.

So as you read this, periodically remind yourself of what you want to optimize for and, perhaps more importantly, what you're willing to give up for it. It may be just as important to live well as it is to live long.

Part I: Delaying death

Up until about a century ago, most of the gains in longevity we made as a species were driven by factors associated with economic growth: improved housing, reductions in malnutrition, and increased sanitation. In the early 20th century, we accepted the germ theory of disease, which drove public health projects like water filtration and chlorination, milk pasteurization, and hand washing. And we came to understand better the nature of infectious disease and vectors—once you understand that mosquitos carry malaria and yellow fever, for instance, or rats plague, you get rid of the mosquitos and the rats.

Water purification alone can explain probably half the mortality reduction in the United States between 1900 and 1940. From the 1930s on, major improvements in life expectancy have come to a large extent from medicine—first antibiotics and vaccines, and later improvements in critical care, which has made a dramatic impact on both blunt and penetrating trauma survival and a modest bump in survival from acute myocardial infarction thanks to emergency medical transportation and early care. At the same time, large gains in life expectancy have also come from structural and environmental shifts like increased vehicle and occupational safety.

But these advances have all reduced *acute* sources of mortality. Today, more than ever, we are being killed by *chronic* conditions. And modern medicine has been woefully inadequate in reversing or preventing chronic conditions.

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Case in point: In the 40-plus years since Richard Nixon declared the "War on Cancer," the U.S. Government alone has spent approximately $155 billion on cancer research—and this does not include the money spent by pharmaceutical companies, nonprofit organizations, and universities that receive non-NIH funding.

The result?

A paltry 5 percent increase in overall cancer survival in the United States.

It seems the best treatment for cancer is not getting it in the first place (as we have seen with the steady reduction in smoking and the commensurate—though time lagged—reduction in lung cancer). Perhaps our greatest success in delaying death from chronic conditions has been in the field of cardiology. And even here, the success has been modest: About half the time a person has their first heart attack, it's a fatal one.

So for all of our great medical and technological advances, especially in the developed world, in reducing death due to acute causes, we've had less success on the chronic disease front. This is clearly evidenced by the Center for Disease Control mortality tables. Two out of three Americans die from four diseases associated strongly with obesity and type 2 diabetes: coronary heart disease (CHD), cerebrovascular disease (CVD), cancer, and neurodegenerative conditions, of which Alzheimer's disease is the most common.

The other one-third of Americans die as a result of many things, including infections (especially the flu), accidents, homicide, suicide, and chronic obstructive pulmonary disease (COPD). This figure (*Top 10 causes of death in the U.S., 2010*) shows the top 10 causes of death in the U.S. These 10 causes account for approximately 90% of all deaths in the U.S. Furthermore, the diseases most associated with obesity and diabetes—the four above—account for ~80% of deaths in the top 10, and ~70% of all deaths.

Now, most of us thinking about this question—*how can I live longer*—are probably not smokers and may be less likely to commit suicide or die from homicide. That means that you and I face a greater risk of dying from The Big Four metabolic diseases: coronary heart disease, cerebrovascular disease, cancer, and Alzheimer's disease

In other words, if you're a middle-aged adult who wishes to delay death and aging as much as possible, **the probability that you will die of a metabolic disease**—those strongly associated with and exacerbated by obesity and type 2 diabetes—**is north of 80 to 90%**. That said, there is strong evidence that obesity, *per se*, is not actually what drives the increased risk alluded to above.

Rather, I believe this risk is driven by hyperinsulinemia and a condition called insulin resistance—the reduced capacity for our cells to dispose of glucose in response to insulin signaling (more on this, below). Indeed, obesity is a proxy for this state—two-thirds of obese individuals are insulin resistant—however nearly 10% of lean individuals are also insulin

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resistant. A number of leaders in the field have been become increasingly critical of this distinction between obesity and insulin resistance.

Streamlining this a bit further, once you've reached your 40s and 50s, and assuming you're not a smoker or a heavy drinker, you don't do IV drugs or engage in super-risky behavior, you are most likely to die from one of three disease *processes*, all of which are exacerbated by insulin resistance:

1. **Cardiovascular or cerebrovascular disease** (these are very similar, except that one impacts the heart, the other the brain)
2. **Malignancy**
3. **Neurodegenerative disease**

A brief word on each follows, but first a short primer on the hormone insulin.

Insulin, *101*

There is one hormone in particular that plays an outsized role in obesity—a hormone that the evidence strongly suggests is a driving force behind some of the most common chronic diseases. That hormone is insulin. When your insulin levels are out of whack, then sickness and disease are sure to follow.

The amount of insulin circulating in your blood stream at any given time is determined in part by the beta-cell of the pancreas, which releases insulin when needed (technically, the beta-cell secretes an inactive molecule—pro-insulin—that gets rapidly cleaved into the *inactive* hormone, C-peptide, and the *active* hormone, insulin). The primary stimulus for insulin secretion is glucose, the simplest or final breakdown product of most carbohydrates. Glucose, contrary to popular belief, is not especially sweet. The sweetness we taste in table sugar, high fructose corn syrup or fruit is more a result of another simple carbohydrate, fructose, which does not elicit the secretion of insulin. Protein also stimulates insulin release by the pancreas.

The purpose of insulin is to 'partition fuel'—which is the technical term for taking the food we eat and putting it in the appropriate storage depot. In this sense, insulin is one of the most anabolic hormones in our body (anabolic hormones promote growth or storage, while catabolic hormones do the opposite). By extension, low levels of insulin have the opposite effect—causing the breakdown of stored energy, our body's fuel. At the risk of over-simplifying a bit, we store *accessible* fuel in two forms:

1. **Glycogen**—the storage from of glucose—which is found in skeletal muscle and the liver (in a ratio of about 75% to 25%, respectively but this varies with several factors). In an adult male the typical storage capacity is approximately 400 grams of glucose (300 in the muscle, 100 in the liver), totaling about 1,600 calories of stored energy.

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2. **Fat**—or more specifically triglycerides contained within fat cells—for which we have a much greater capacity for storage (i.e., relatively unbounded). Even a lean adult may carry 10 kg of fat in their body, totaling 90,000 calories of stored energy.

Insulin promotes both the storage of glucose and fat; and by extension, low levels of insulin promote the breakdown of glycogen and stored fat. But the story is more nuanced. Insulin also determines how fuel is partitioned in our body. Two people can consume the exact same meal with equal amounts of fat and glucose, and yet store and metabolize different amounts of both.

Why?

Therein lies the great variation in humans—from person to person we release different amounts of insulin under identical glucose loads and our cells respond differently to similar levels of insulin secretion.

Part of this difference is genetic, but most of this difference results from the slow accumulation of changes in body driven by what we eat, how we sleep, how we exercise, how we manage stress, other hormones in our body, and even drugs we take—as we shall soon see.

Alzheimer's disease

Though not readily appreciated in the mainstream, a growing number of scientists and neurobiologists are now referring to Alzheimer's disease as 'brain diabetes' or 'type 3 diabetes.' Type 2 diabetes is thought of as a disease that disrupts the body's ability to take glucose and safely usher it into fat cells or glycogen stores. And now a small but growing number of experts are reaching the conclusion that Alzheimer's disease is the result of a very similar process in the brain: a failure to get glucose into neurons, the most energy-demanding cells in the body (our brains make up less than 5% of our body weight, yet account for north of 20% of our energy requirement).

In very good animal models of Alzheimer's disease, administering large doses of intravenous glucose and insulin transiently improves cognitive function.. But this offers no long-term treatment. Anecdotally, a number of sources have reported in humans a marked improvement in symptoms with a combination of dietary glucose restriction and/or medium chain triglyceride (MCT) oil administration—both ways to simultaneously reduce neuronal dependence on glucose and increase production of endogenous ketones (an alternative fuel for neurons). In animal models of Alzheimer's disease, this improvement in cognitive function has also been demonstrated with the administration of synthetic ketones, absent any reduction in glucose or addition of insulin.

Some authorities have argued that Alzheimer's disease is the inevitable consequence of our species living longer—a so-called price for our longevity success—while others have suggested it's an epidemic on its own. Is the surge of Alzheimer's disease just a consequence of living

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longer, or an epidemic alongside two others (obesity and type 2 diabetes)? My vote is with the latter, since the rate of increase in Alzheimer's disease—even with the increased emphasis on early diagnosis—is considerably steeper than the incremental slope of our longevity curve.

Between 1950 and 2010, longevity increased by **0.6% per year** in the U.S., while the prevalence of Alzheimer's disease increased by **2.6% per year**. That said, even if part of the increase in Alzheimer's disease is driven by awareness and more attention to diagnosis, it's hard to argue with this fact: Anything we can do to avoid Alzheimer's disease and other forms of neurodegeneration is likely a better strategy than looking for ways to treat it, at least in the foreseeable future.

Cancer

In 1924, a scientist named Otto Warburg happened upon a counterintuitive finding. Cancer cells, even in the presence of ample oxygen, underwent a type of metabolism that cells reserved for rapid energy demand—anaerobic metabolism—which does not utilize oxygen. In fact, even when cancer cells were given *additional* oxygen, they still almost uniformly defaulted into using only glucose, without oxygen, to make ATP[1] via the *anaerobic* pathway. This is counterintuitive because this way of making ATP is typically a last resort for cells, not a default, due to the very poor yield of ATP relative to aerobic metabolism, which uses oxygen to metabolize glucose or fat through a part of the cell called the mitochondria.

This observation begs a logical question? Do cancer cells do this because it's all they can do? Or do they deliberately 'choose' to do this? I'm not sure the answer is entirely clear or even required to answer the more important question: *Can this metabolic quirk be exploited?*

With the exception of lung cancer (the #2 cause of cancer death in both men and women, though primarily resulting from tobacco use), most cancers are primarily fed by glucose—evidenced by not only the Warburg effect, but the success of FDG-PET[2] scans for cancer detection—and appear to have their kinetics governed by insulin signaling and that of insulin-like growth factor-1 (IGF-1).

Outside of lung cancer, the cancers that are most deadly—breast, prostate, colon, pancreatic, ovarian, endometrial, glioblastoma multiforme (GBM)—appear to all share the same metabolic

[1] Adenosine triphosphate, the 'currency' of energy used by the body. As its name suggests, this molecule has three (tri) phosphates. Energy is liberated for use when the body converts ATP to ADP (adenosine diphosphate), by cutting off one of the phosphate ions in exchange for energy.

[2] A type of 'functional' radiographic study, often called a 'pet scan' for short, used to detect cancer in patients with a suspected tumor burden (this test can't effectively detect small amounts of cancer and only works for 'established' cancers). F18 is substituted for -OH on glucose molecules, making something called 2-fluoro-2-deoxy-D-glucose (FDG), an analog of glucose. This molecule is detectable by PET scanners (because of the F18) and shows which parts of the body are most preferentially using glucose.

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quirk. This quirk, though not ubiquitous in all of these cancers, is present enough that it should be exploitable. In other words, reducing insulin resistance—ensuring that your cells are as facile as possible at taking in glucose in response to insulin—is an essential strategy for reducing your risk of cancer and neurodegenerative disease. Like Alzheimer's disease, *curative* treatments for cancer have been few. Outside of some forms of leukemia and lymphoma, and certain testicular cancers and a rare gastrointestinal cancer, little progress has been made in *curing* metastatic cancer, the ultimate benchmark of cancer treatment. Today the best shot at 'beating' cancer is avoiding it.

Once a person has cancer, absent a breakthrough in treatment, there may be better treatment options out there than simply standard-of-care (i.e., a combination of surgery, chemotherapy, and radiation). Two other modalities I suspect will play an increasing role in cancer treatment are *metabolic therapies* and *immune-based therapies* (which are already playing a role in some cancers—melanoma and renal cell cancer).

Think of cancer as a stool with 5 legs. To beat it, given its resilient traits, we need to whack all the legs as hard as possible: (i) chemotherapy and radiation as needed to disrupt the cancer cell's ability to replicate its DNA; (ii) hormonal therapy where appropriate; (iii) hyperbaric oxygen to challenge unstable mitochondria; (iv) drugs and diet to reduce glucose, insulin, and IGF-1 for cancers that rely heavily on glucose (e.g., metformin, ketogenic diet, exogenous ketones); and (v) adoptive immunotherapy, in cases where cancer antigens can be identified.

In the coming decade I hope to see clinical trials aimed at testing this hypothesis. Continuing our current strategy—the status quo—doesn't seem especially promising. That's why in my own practice I'm using every tool that I have to give my patients a fighting chance.

Cardiovascular and cerebrovascular disease

What about the No. 1 killer of Americans, heart disease and stroke?

We have all been led to believe that the underlying issue is too much LDL cholesterol—which is essentially the amount of cholesterol carried in your low-density lipoproteins (LDL). But a growing amount of research suggests that this is not entirely true.

Every LDL particle carries on its surface a type of protein known as apoB, which distinguishes LDL particles—those that cause heart disease—from, say, HDL particles. Allan Sniderman, the scientist who helped shape our understanding of apoB, has written extensively about the risk of heart disease (and stroke) and has proposed a *causal exposure model* (*Causal exposure model...*). This model suggests that there is no greater risk factor for heart disease than *age*. Why? Because the passage of time and the resulting exposure of these apoB particles to the endothelium—the lining of our arteries—is the defining event of atherosclerosis.

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Briefly, this is what causes atherosclerosis (at the molecular level): apoB-bearing lipoproteins (mostly LDL particles, but also VLDL particles and Lp(a) particles in those with high numbers of them) traffic cholesterol throughout the body. When they collide with the arterial endothelium (this phenomenon occurs in all arteries, but the impact is greatest in the heart and brain because of artery size and organ dependence on oxygen), some of them penetrate the tight junctions of the endothelium and make their way into the sub-endothelial space (the zone underneath the endothelial later of the artery). Once there, a subset of these particles are retained (due to an inflammatory process) and for reasons not entirely clear, they deposit their cholesterol 'cargo' there, which is then, often, oxidized.

And so begins the vicious cycle of atherosclerosis. As more cholesterol, or 'sterols,' get oxidized, the endothelium becomes easier and easier to penetrate by additional apoB particles. So the feed-forward loop progresses until a critical plaque is unstable enough to shear off and result in a critical ischemic event, such as a heart attack, stroke, or death.

Most patients are mismanaged with respect to cardiovascular disease because most physicians don't actually understand how atherosclerotic heart disease works. Their doctors manage their LDL cholesterol (or worse, their HDL cholesterol) without even knowing what their LDL particle number is, what their Lp(a) particle numbers are, or how much inflammation they have in their body. Many patients may even be told their cholesterol levels are fine and their risk of heart disease low, even as they unknowingly walk around with a dangerously high particle number.

Focusing on LDL cholesterol—not LDL particles—overlooks the underlying driver of atherosclerosis.

The reason Sniderman's model shows that the passage of time is the crucial risk for cardiovascular disease is because of continuous endothelial exposure to apoB. Hence, to delay death as long as possible due to CHD/CVD one must take steps to reduce apoB, reduce inflammation, reduce hypercoagulation, and reduce all things that sensitize the endothelium to these insults. The overwhelming majority of adults are never given this information, which means two things.

The bad news most people are still going to die of this disease process because they are being badly mismanaged.

The good news this is a highly preventable process, if you know what to look for and how to treat it early and aggressively.

Superimposed on all of this, a robust family history (to get a sense of a person's genetic predisposition to certain diseases), coupled with a straightforward genetic assessment (to actually determine the presence or absence of genes known to increase risk for metabolic disease), can further estimate a person's risk of 'most likely cause of death' and thereby focus preventative measures against a particular outcome or set of outcomes.

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Two of the most important genetically determined features I look for in my patients when it comes to CHD are apoE genotype and Lp(a)-P.

The latter is a genetically determined type of lipoprotein that is especially atherogenic and likely responsible for premature heart disease in one out of five people. The former is a gene that codes for proteins responsible for cholesterol transport, among other things, and is highly implicated in AD and CHD.

The 'normal' variant of apoE is 3/3—meaning two copies of the number 3 allele—but there also exist number 2 and number 4 alleles. The 4 allele confers greater risk of CHD and AD in non-linear fashion—people with a 3/4 pattern have a modest increase in risk, while those with the 4/4 pattern have a significantly greater risk—upwards of 20-fold compared to those with 3/3.[3]

In addition, a host of other genes suggest increased, or decreased, risk of CHD/CVD, cancer, and AD. Information is power, and the sooner one knows their risks, the sooner they can begin the process of pushing back their so-called fate.

In short, to delay the onset of death as much as possible—i.e., to fight aging—one must minimize the biological forces that lead to the Big Four chronic diseases. The decision about how to prioritize this effort is heavily influenced by genetic factors (in-depth family history and select genetic testing).

The bottom up approach to longevity

But there is at least one other way to think about longevity. If the above approach—reverse-engineering how to delay death by looking specifically at the causes of death—is a top down approach, it's worth discussing the bottom up approach: How does behavior X or action Y impact your longevity? For example, you may be asking at this point, "*What about drinking red wine?*" or "*What about caloric restriction?*"

After surveying the literature addressing this question, I believe the following statements are accurate:

1. The single greatest factor that determines your longevity may be your genes—if your parents lived to be 100, you can smoke all day long and likely make it to 90. At the risk of oversimplifying, there are three 'archetypes' of genetic patterns for what

[3] It is not clear if this 20-fold increase is risk for heart disease is present once normalized or 'corrected' for LDL-P, because no such study has been in done. In other words, if someone with apoE 4/4 has the same LDL-P as someone with apoE 3/3, are they still at increased relative risk? In speaking with both Tom Dayspring and Allan Sniderman both believe—emphatically—that once LDL-P (or apoB) is corrected for, apoE genotype does not predict risk for heart disease. The same, however, does not appear true for Alzheimer's disease, though the story is more complicated here based on recent literature suggesting the plasma (blood) levels of apoE are more predictive of Alzheimer's disease than actual genotype.

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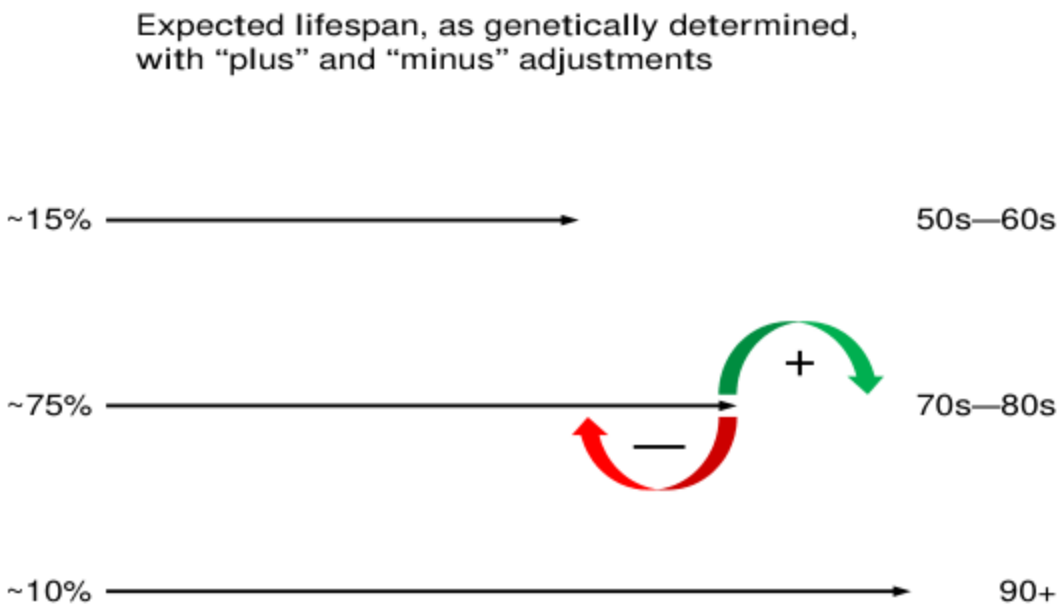
we'll call expected lifespan (EL): short, medium, and long. To illustrate further, consider the following figure:



About 15 percent of people are genetically 'programmed' to die in their sixth or seventh decade (50s to 60s); about 10 percent of people are genetically 'programmed' to live into their 90s or beyond. The rest of the population is somewhere in the middle, which is typically where the average life expectancy resides.

But that's not the whole story, obviously. You are not simply the sum of your genes. The actions we take—what we eat, how we exercise, how we sleep, how we cope with stress, and a few other actions—coupled with when we implement these actions (earlier is better, obviously) determine the "plus" or "minus" we apply to our genetically inherited EL.

2. Most 'magic bullets' that get lots of press and shelf space at supplement stores (e.g., resveratrol) turn out to be of no efficacy at all when repeatedly tested in controlled trials. In other words, save your money.

3. Caloric restriction (CR) is probably the greatest action you can take to impact longevity (shy of choosing long-living parents), but the question is why? Is it the actual reduction in the total number of calories that leads to the effect? Or is it the reduction in a subset of calories also reduced by CR (e.g., a reduction in the specific macronutrients that are known to raise insulin, insulin-like growth factor, and growth hormone)?

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4. If any drug (or class of drug) being evaluated today is going to have an effect on longevity, it's a drug that inhibits the *mammalian target of rapamycin* (mTOR). I'll explain why.

A brief word on caloric restriction and mTOR inhibition

Caloric restriction

Though not seen uniformly across all species (e.g., significant longevity response seen in rats and ringworms; little to none seen in many strains of mice), it has been widely documented that 20 to 40 percent caloric restriction (CR) increases longevity in many species by up to 30 percent (excluding, of course, the species of interest—humans—for which we don't have experimental evidence). So there are really two important questions about CR: (i) *why does CR work in some species* (sub question: and why not others)? and (ii) *does CR work in humans?*

My poring obsessively over the literature on this topic has led me to a few conclusions—and interpolations—with respect to CR:

1. There is a paradox at play—the upside of CR may be due to the hormonal impact (more on that in a moment) than on the accompanying weight loss, which may actually be a *downside*. For example, in mice (a species that typically doesn't respond as favorably as others to CR), the mice that lose the *least* fat mass while being calorically restricted survive the longest, relative to those that lose more fat mass (and weight). Furthermore, there is a bit of an artifact in animal studies of CR—they live in an artificial environment. As such, they are insulated from natural consequences of caloric restriction that may offset the hormonal benefit of CR. For example, because they are not in the wild, they are less susceptible to temperature intolerance, the effects of reduced muscle mass and osteoporosis, and a reduction in their immune strength.

2. The efficacy of CR *may* be more in response to a specific dietary component being restricted (a so-called 'DR' for 'dietary restriction' in the literature) under most conditions of CR. For example, when you reduce total calories, all calories are typically reduced more or less equally. As such, it's not clear if the benefit of CR is due to the total number of calories being reduced or the reduction in a *specific type* of those calories. If it is the latter, the two prime suspects are sugars and simple carbohydrates, due to their effects on insulin, insulin-like growth factor (IGF), and growth hormone (GH). Some literature suggests modest protein restriction may increase cellular longevity via its effect on fibroblast growth factor 21 (FGF 21), or possibly via the effect of protein on IGF or mTOR (more in a moment).

3. There is evidence in mammals (though not ringworms) for the idea that DR may be more important than CR in promoting longevity. In other words, there is evidence that it's the restriction of a type of calorie more than total calories that is providing the longevity boost. Mice *without* GH receptors do not experience longevity gains when fed a diet that reduces

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GH and IGF, while mice *with* GH receptors do experience an increase in longevity with a dietary restriction that lowers GH and IGF (without necessarily restricting overall calories). Furthermore, experiments in primates have also suggested that CR that uniformly restricts all parts of the diet increases longevity, while some forms of DR—specifically, calorie-restricted diets that keep sugars high—do not increase longevity.

4. It seems that slowing the aging process may be predicated on slowing the rate of protein synthesis. However, this seems age-dependent—inhibiting protein synthesis in the young is maladaptive for species survival.

5. Lastly, and perhaps most importantly, the benefit of CR (assuming it has benefit over DR—still an open question) seems to vanish, if not become a detriment, with extreme CR (i.e., 40% or more). While such an approach to CR may increase *cellular health*—the ability for a cell to replicate and preserve the integrity of its DNA—it may actually cause more harm to *overall health*—the survival of the organism. For example, extreme CR may weaken the immune system, making it less able to overcome infection, and reduce muscle mass and bone density, making us more vulnerable to injury and trauma.

Mammalian target of rapamycin (mTOR)

Mammalian target of rapamycin (mTOR) is a protein—found inside of cells—critical for cell growth, cell proliferation, protein synthesis, cellular stress response, a process called autophagy (cells in the body eating themselves, which is also regulated by insulin), and other important processes that regulate cell survival. One of the reasons mTOR inhibition is particularly compelling is its mechanistic overlap with the CR and DR approaches that reduce insulin and IGF/GH. In fact, mTOR is what is known as a "downstream" integrator of the signals from IGF, GH, and specific amino acids. That is, it incorporates the signals from these "upstream" signals—e.g., cellular energy levels are high or low—and ramps up or down essential cellular functions, such as growth and proliferation.

Oversimplifying a bit, inhibition of mTOR after early life development appears to increase longevity and even rejuvenate stem cells in most animal models (excluding primates). Inasmuch as CR and/or DR increase longevity, it may be that both approaches—directly inhibiting mTOR with a drug like rapamycin and indirectly inhibiting mTOR via dietary strategies that reduce insulin/IGF/GH as upstream signals—affect similar common pathways. Furthermore, mTOR inhibition or activation may have different effects on longevity depending on the type of cell. Specifically, mTOR inhibition appears to promote longevity in liver and fat cells, but not necessarily in muscle cells.

Yet another observation that bolsters the case for mTOR playing a critical role in longevity is the overlap with another cellular pathway that is increasingly important in cancer treatment and prevention—the AMP kinase pathway. When cellular energy is low—when ATP is heavily

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being converted to ADP and eventually AMP—the ratio of AMP to ATP in the cell is high.[4] This high AMP-to-ATP ratio tells the cell—be it a liver, muscle, or brain cell—that energy is scarce.

Enter an enzyme called AMP-activated kinase (commonly referred to as AMP-kinase or AMPK). AMPK is one of the most important enzymes in cellular energy homeostasis. When AMPK is activated a chain reaction of important processes take place: the liver starts turning fat into ketones, the cell is inhibited from forming cholesterol, from turning carbohydrates into fats, and from fat storage, and a host of other changes that aim to stop energy storage and enhance energy creation from existing stores. And AMP kinase also inhibits mTOR complex 1, which is one of the two complexes that make up mTOR.

Drugs like metformin, which directly activate AMP kinase, result in reduced hepatic glucose output (and therefore less circulating glucose and insulin, which is why it's prescribed for people with type 2 diabetes). So both CR/DR and drugs that mimic some of its effects are indirectly inhibiting mTOR, which may explain, at least in part, the longevity enhancement of a drug like rapamycin, which directly inhibits mTOR.

Basically, CR, AMPK activation (through CR or drugs), mTOR inhibition (through AMPK activation or drugs) all point in the same direction: cellular longevity.

How this translates into diet and nutrition

Based on the best scientific evidence we have, the ideal diet to promote longevity is likely a 10 to 20% calorie-restricted 'clean' ketogenenic diet, which limits carbohydrate consumption to berries and vegetables; keeps protein to no more than about 80 g/day and relies more on organ meat that 'muscle meat' of the animal. It includes mostly saturated, monounsaturated, and omega-3 polyunsaturated fats—the kinds found in meat, eggs, fish, olive oil and nuts—rather than the omega-6 polyunsaturated fats found in highly processed vegetable oils, like corn, sunflower and soybean oil. And it also restricts the trans fats found in heavily processed foods like cookies, potato chips, pastries and packaged snacks. One of the goals is to keep the ratio of omega-6 to omega-3 polyunsaturated fat as low as possible, because the omega-6 fats in vegetable and seed oils promote inflammation—among other things—while omega-3 fats have the reverse effect. Such a diet, in addition to being modestly restricted in calories, probably involves some form of fasting, such as one or two 24-hour fasts per week.

This diet would need to be rich in essential nutrients and avoid contaminants of preparation (e.g., over-cooking). This is the diet strongly supported by scientific evidence, but at the same time it may not be uniformly true for all people. Some people may tolerate more protein and/or carbohydrate than others. Conversely, others may tolerate less fat. Ancestry seems to play a big

[4] Recall, ATP—the so-called energy currency of the cell—has 3 phosphates (hence the name adenosine *tri*phosphate) and therefore more energy than ADP (2 phosphates) and AMP (one phosphate). Transiting ATP to ADP and ADP to AMP, "liberates" phosphates and therefore energy for the cell to use.

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role. For example, descendants of northern Europeans may be more genetically equipped to process starch than, say, those of African descent.

The 'optimal' diet for longevity may not be an easy one for some people to follow. But I believe one can achieve much of its theoretical benefit from less extreme diets that capture some of the most important features of this extreme one. I tried much of the above dietary approach for 6 months in combination with intermittent fasting. I consumed one to two meals per day totaling about 70 to 75% of total energy expenditure at the outset of the 'experiment,' which meant consuming 2,500 to 3,000 kcal/day instead of the 3,600 to 4,000 kcal/day I typically did for weight stability. In the process I lost 8 pounds and my resting energy expenditure reduced to match my reduced intake – in other words, the weight that I lost did not bounce back a short time later, which is what often happens after a diet. Ultimately only time will tell whether this dietary change increased my longevity. But it did impede my physical and mental performance (and happiness!). I was often hungry, especially late in the day and when I went to bed. So while this dietary strategy may have been beneficial to my cellular health, it wasn't worth the trade-off to me.

The good news is that I don't think we need a diet as restrictive as the one I tried for 6 months to approach the theoretical limits of our genetic potential. As Denise Minger summarized in her book, *Death By Food Pyramid*, Weston A. Price's survey of populations most free from metabolic disease—the Swiss of Loetschental Valley, the Gaelics in Hebrides, the Eskimos of Alaska, the Native American Indians of the Rocky Mountains, the tribes in eastern and central Africa, the Australian Aborigines, the Maori of New Zealand, and others—noted great variation in diet (e.g., more fat vs. less, more starch vs. less), but there were *three characteristics* preserved by all groups, a clue that such features of our diet today can minimize our risk of metabolic disease:

1. The diets were entirely free of refined sugar and refined carbohydrates
2. The diets were very low in omega-6 polyunsaturated fats (i.e., those found in the now ubiquitous vegetable oils)
3. The diets were dense in nutrient content

Interestingly, not one of the long-living/disease-free populations lived entirely free of meat or animal products, which seems to imply that the purported life-extending properties of plant-based eating may have less to do with avoiding animal protein and fat and more to do with adherence to the above three features. (With apologies to my vegan friends. But the facts are the facts).

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Part II: Optimizing life

I've often wondered what the main difference is between me today (at 42) and me at 18 when I felt like Superman. I'm sure everyone can relate to that evolution—less energy, longer time to recover from workouts, loss of ability to stay lean while eating virtually anything, maybe even less irritable.

One of the main differences between the 18-year-old version of me and the 42-year-old version is a change in my hormones—something that happens to all of us.

Hormones, which largely regulate the physiologic processes controlling the body, can be divided into four broad categories, or axes:

1. Sex hormones (e.g., testosterone, estrogen, DHT)
2. Adrenal hormones (e.g., cortisol, epinephrine, norepinephrine)
3. Thyroid hormones (e.g., T3, T4, rT3)
4. Fuel partitioning hormones (e.g., insulin, glucagon, cortisol)

There is overlap between these categories (e.g., cortisol is a stress hormone, but it also factors heavily into fuel partitioning) and these four axes all act on each other, so when one axis is off, others are impacted. So while I'm going to oversimplify greatly to get my point across, don't assume these endocrine systems act independently. In fact, nothing could be further from the truth. Though I describe them as four axes, it's probably more accurate to think of them as four dimensions of a complex web—if you push or pull on one string, you invariably distort the others.

As we get older, we move away from the optimal state in each of these axes. Though somewhat oversimplified, it's safe to say getting older generally mean*s* getting *weaker*, *fatter*, *slower*, *colder*, and *less energetic*.

A very brief description of how each endocrine axis contributes to this follows:

1. **Sex hormones**
   In men, testosterone and free testosterone (the fraction of testosterone that is not bound by sex hormone binding globulin (SHBG) and therefore is biologically active) are gradually reduced with time, due to (i) reduced testosterone production, (ii) increased estrogen conversion and concomitant rise of SHBG, which leaves less testosterone to be 'free' for biologic activity, (iii) reduced conversion of testosterone into DHT (a more potent androgen), and (iv) resulting free testosterone. In women, changes in sex hormones are most extreme during the peri-menopausal time period, when estrogen and progesterone cycling reduces, along with absolute levels of all androgens, including testosterone (important for women, too). In both men and women, these changes typically

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result in reduced lean body mass, increased fat mass, reduced energy, altered libido, and other changes that negatively impact resilience and performance.

2. **Adrenal hormones**
   As we age, we tend to produce too much cortisol (in response, typically, to stress), too little cortisol (adrenal fatigue), or the rhythm in which we produce it gets thrown off (often due to sleep disturbances). All of these states result in suboptimal human performance and in the case of excess cortisol production, unfavorable fuel partitioning (e.g., more fat storage).

3. **Thyroid hormones**
   Aging—along with stress, changes in weight, depression, sleep deprivation, etc.—increases conversion of T4 (inactive thyroid hormone) to reverse T3 ('anti-thyroid hormone') instead of the active hormone, T3. The result is reduced energy, mood alterations, reduced metabolic rate, cold intolerance, and a host of other subtle symptoms that are typically classified as 'just getting old.'

4. **Fuel partitioning hormones**
   As we age, our cells become less sensitive to insulin, the hormone that most regulates the flux of fat into and out of fat cells. We also, likely, increase expression of lipoprotein lipase (LPL) on fat cells, increasing fat storage, while decreasing LPL expression on muscle cells, decreasing fat oxidation. For most people—between 60 and 80% in my estimation—the energy 'currency' of body shifts further to glucose dependency (vs. fat utilization). This is bad for many reasons, not the least of which is this: you store more fat and rely more heavily on glucose for energy (remember the point above about cancer feeding off glucose).

All of these hormones can be manipulated, either *directly* (hormone replacement therapy or direct hormone suppression) or *indirectly* (pro-hormones, nutrition, sleep, exercise, meditation). My belief is that **the closer one can approximate the hormonal milieu of youth, those closer one can approximate an optimal state with respect to performance and quality of life.** The closer you can get the hormones (and their accompanying enzymes) to replicate their actions in your 20s the more likely you are to feel as though you're still there (for better or worse).

The underappreciated role of sleep

A discussion of sleep can really be placed into either Part I (delaying death) or Part II (optimizing life). Why? Sleep deprivation appears to directly contribute to insulin resistance. One very well controlled (albeit small) experiment found that restricting subjects to 4 hours of

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sleep per night for just 4 nights impaired glucose disposal using the gold standard test—frequently sampled intravenous glucose tolerance test (FSIVGTT)—along with a molecular assay performed on biopsies of the subjects' fat cells. A very good overview of the metabolic impacts of sleep deprivation can be seen in this video by Dr. Eve Van Cauter.

Furthermore, chronic sleep deprivation—even just an hour per night—over long enough periods of time results in deleterious functional changes in performance (e.g., memory, cognition, motor control). As my mentor on the science of sleep, Kirk Parsley, discussed in this talk mild sleep deprivation mimics the impairment of alcohol consumption.

So in addition to impairing your ability to partition fuel, taxing your adrenal system, and impairing memory formation and motor control, failure to sleep sufficiently endangers your life just as driving with a blood alcohol level of, say, 0.04% or more would.

As Kirk is quick to point out when 'type A' folks push back on the notion that sleep is especially important (as I used to), sleep must have been a very dangerous activity for our ancestors—spending 30-35% of our lives effectively unconscious makes avoiding predators a challenge—yet we never selected (in an evolutionary sense) a way out of it. (As an aside, the best evidence today suggests that while our ancestors slept approximately 8 hours each day, they did in two chunks of about 4 hour each interrupted by a midnight meal.) The fact that this need for approximately 8 hours of sleep each day didn't go away is pretty a good sign that sleep matters, and probably a lot. Fortunately, there are half a dozen relatively easy changes one can make in sleep hygiene (e.g., reduction of blue light in the hours before sleep; complete darkness in room; absence of electronics in bed; appropriate temperature of room) to improve sleep duration and quality. If these are insufficient, hormones and supplements (e.g., vitamin D3, T4, L-DOPA, melatonin) can help bridge the gap to excellent sleep.

But step one is accepting that you need to sleep (probably more than you're doing now).

The confusion around exercise

My intuition—informed by a lot of emerging evidence—is that our beliefs about exercise may be as arcane as our beliefs about nutrition and hormones. More than anything else, to have a thoughtful discussion on exercise, one must differentiate between two states that are almost always confused:
State #1 performance enhancement/ optimization vs. **State #2 sickness/illness aversion** (i.e., anti-aging). There is no reason to prefer one state over the other, but it's critical to understand the distinction if you want to have a shot at excelling in either.

Here's an (extreme) example: The training required for one to win the Tour de France (TdF) or an Olympic event is 100% focused on State #1 and almost without exception runs at best orthogonal and at worst anti-parallel to State #2. Virtually every endocrine system in a cyclist

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post-TdF is 'broken.' Even in me and other non-world class or elite athletes, extreme activity (e.g., marathon swims, Ironman triathlons) produces a level of inflammation in the body comparable to sepsis (i.e., systemic inflammatory response syndrome) or severe trauma.

Performance maximization, such as in the examples above, requires a very specific type of muscular and nervous system stimulus. Most people have never experienced the specificity and intensity of that stimulation, yet they continue to believe they are optimizing performance (while not doing so) and are unknowingly missing an opportunity to improve their health. I suspect the majority of people who exercise (or 'train') are in this no-man's land: they don't train hard enough or specifically enough to enhance performance, yet their training also runs counter to the principles of health optimization.

Conversely, the exercise principles I believe is best to slow aging as much as possible doesn't necessarily make you any better equipped to win a race or athletic event. So again, we have a trade-off.

With that principle in mind, and assuming we're optimizing for State #2, given the theme of this discussion, here are my views on the role of exercise and physical activity in the avoidance of aging/delay of death/optimization of life.

1. Constant 'cardio' probably does little to avoid aging and may actually *accelerate inflammation* in susceptible individuals.

2. Though impossible to test in humans in a prospective randomized fashion, evidence is mounting that heavy amounts of aerobic activity—especially long bouts of the type of exertion that demands maximum aerobic capacity (i.e., you are too exhausted to speak)—may result in right-sided cardiac dilatation (stretching), which may be the driver of the paradoxical rise we're seeing in dysrhythmia (e.g., atrial fibrillation at best; fatal ventricular tachycardia at worst) in athletes. Simply put, the right side of the heart—whose role is only to pump blood against the low pressure pulmonary system—cannot accommodate prolonged exposure to 20-30 liter per minute cardiac outputs (up to 5 or 6 times the cardiac output at rest). While the muscular left side can, and does, grow larger in response, the right side cannot. Instead, repetitive dilatation of the right atrium, in susceptive individuals, alters the electrical conduction system of the heart, which leads to these arrhythmias. James O'Keefe, a thoughtful cardiologist on this topic has written about this unintended consequence of exercise extensively. Here are links to two of his papers on this topic (*Excessive endurance exercise...* and *Potential adverse CV effects...*).

3. Preserving muscle mass as we age is an important step to ward off aging. Muscle mass preservation not only prevents injury, but also increases glucose disposal—less so during exercise, which is also true of modest aerobic activity, but more so at rest by improving muscle insulin sensitivity—which is important for reducing the risk of the Big Four metabolic diseases. This is true in both men and women. In addition to building muscle mass and preserving it as we age, increasing and maintaining mitochondrial density may (no

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experiment has been that I am aware of to test this, but my clinical experience finds it to be so) provide accretive benefits when combined with a correct dietary strategy for maintaining metabolic flexibility and glucose disposal. In other words, combining a correct dietary strategy to a correct exercise strategy may produce more than additive effects.

4. To build and preserve muscle mass (for both men and women) requires a specific muscle *stimulus*—progressive resistance training with heavy enough weights to ensure recruitment of the most forceful muscle fibers, type IIB muscle fibers (the so-called 'fast-twitch' fibers, though this name is a misnomer—they twitch at the same rate as type I, or slow twitch, fibers). There are many ways to achieve this stimulus with varying degrees of efficiency—traditional free weights, Crossfit workouts and its derivatives, and even exercises with only one's bodyweight. While my vote for 'the best' free weight exercise a human being can do is probably the hex bar deadlift, for most people this is not a realistic option and the belief that it is necessary should never serve as a deterrent to participation in strength training. As far as best bang for the buck, I prefer (especially for those without years of experience correcting practicing powerlifting—the squat, the deadlift, and the bench press—and those with injuries) the super slow protocol. Remember, goal number one is to avoid injury (sorry Crossfit) before proceeding to goal number two—muscle building.

5. Any activity that significantly increases the risk for an orthopedic injury should be minimized as we get older (e.g., excessive running, rock climbing, mogul skiing in folks who don't really understand how to absorb the bumps)—the worst thing that can happen is you get hurt and can't do anything.

6. Some activity should be present to maintain joint integrity and flexibility. Whether yoga in its various forms is the right choice, I'm not experienced enough to say, but dynamic movements that increase (and maintain) flexibility appear to preserve movement better that static ones.

7. Though I am unaware of clinical data to point to, my experience (personal and professional) suggests that some form of deep tissue work—ideally weekly—from a practitioner who has a sound understanding of kinesiology and repetitive use injury goes a long way to prevent injury and may even increase adaptation to physical stress.

8. Lastly, keep in mind the following two facts about our species, according to Harvard anthropologist, Daniel Lieberman: (i) over 24 hours there is no animal on earth that can cover more ground than humans (we get our butts handed to us over shorter distances, but we can walk forever), and the best estimates of anthropologists suggest ancient humans walked an average of about 6 miles or so per day. Without any great experiment to point to, I would argue this: *if you have the chance to walk, do so—we gave up a lot (evolutionarily) to be especially good at it.*

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Summary

The fight against aging is a war on two fronts: a fight to delay death as long as possible; and a fight to revert life, hormonally and metabolically, as closely as possible to what it was when we were at our most vibrant, typically in our late teens and early 20s. These efforts, however, can't be treated as absolutes or additive extremes. The interventions that may most significantly increase cellular longevity may not produce optimal performance for enjoyment of life (it's hard to feel great when you're too tired to get out of bed). Additionally, interventions that may increase the optimization and performance of life may accelerate cellular aging.

Which brings us back to the question we started with. Are we optimizing only to maximize the years of life? Or are we optimizing to increase years of life within the constraints of something else—some measure of happiness? For me, it's definitely the latter, and as such, I believe there are six actions/behaviors we can take control of to tilt the balance in our favor to **live longer** (not necessarily the absolute-bar-none-longest), **perform better**, **be more productive**, and **ideally enjoy life as much as possible by minimizing forces that oppose our physical robustness** (this list excludes, of course, the most important feature—genetic selection—which we have no control over).

Very briefly, here they are:

1. **Nutrition**
    i. Maximize insulin sensitivity and capacity for glucose disposal; keep IGF low (requires varying amount of carbohydrate and sugar restriction, depending on genetic predisposition);
    ii. Ensure micronutrient balance
    iii. Consume protein in moderation, in an attempt to minimize gluconeogenesis (turning protein into glucose) and accelerated protein synthesis.
2. **Sleep**
    i. Optimize duration (for virtually all people this is between 7.5 and 8.5 hours per night despite claims to the contrary by those who feel 'fine' with less sleep);
    ii. Use appropriate sleep hygiene to increase likelihood of good sleep quality (i.e., sufficient stage IV sleep);
    iii. When necessary, utilize sleep supplements that aid in sleep (note: this does not include horrible drugs like Ambien), such as melatonin, GABA, and phosphatidylserine;
    iv. Ensure some measure of consistency in sleep and wake time.

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3. **Exercise and mobility**
    i. Focus on avoiding injury—orthopedic or cardiac;
    ii. Use appropriate strength training to maximize mitochondrial density and subsequent capacity for glucose disposal;
    iii. Emphasize strength building and preservation of lean mass as you age;
    iv. Prophylactically utilize some form of deep tissue massage/manipulation, combined with body kinematics for injury avoidance and maintenance of body mobility.
4. **Stress management**
    i. Take deliberate action to reduce response to stress (I can't say "reduce stress" any more than I can say "change your eye color," because I'm not sure the Type A folks that read this can realistically reduce the force in life that produce the stress response, shy of a life change. Rather, I believe we can take very deliberate steps to reduce our negative *responses* to stress);
    ii. Broadly speaking there are three forms of meditation (*Focused attention*—e.g., zazen; *Open monitoring*—e.g., mindfulness; and *Transcendental meditation*—e.g., automatic self-transcending). I suspect people who are able to find a method that can be incorporated into regular practice find benefit in stress response. The key is figuring out which one works best for you;
    iii. For some, exercise and/or yoga serve this purpose, though probably for different reasons;
    iv. Sleep optimization plays a significant role in feedback on this response.
5. **Sense of purpose and social support**
    i. Needs to be addressed
6. **Hormone optimization**
    i. Using pro-hormones and hormones, as necessary, optimize performance with particular attention to *thyroid function* (typically replacement); *adrenal function* (typically support, but sometimes short periods of replacement; sometimes suppression late in day); and *androgen levels* (which is often less about direct replacement of androgens, and more often about minor replacement of androgens coupled with pathway blockade and shunting);

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ii. It's very difficult to correct hormonal deficiencies without correcting sleep, and vice versa (e.g., T4 deficiency impairs sleep; poor sleep impairs androgen replenishment);

iii. The subtlety of hormonal optimization is that symptoms matter more than numbers. For example, replacement of thyroid hormone should be guided more by symptoms (e.g., depression, constipation, poor sleep, cold intolerance) than by TSH level (i.e., the lab value typically used to determine if thyroid replacement is necessary);

iv. Unlike pharmacotherapy (#6, below) which *only* suffers from suboptimal clinical trial data, the clinical trials in hormone replacement are *especially* plagued by poor design (and poor interpretations)—cases in point: HRT in post-menopausal women without attention to the mode of estrogen delivery; use of immediate-release T3 in hypothyroid patients; inattention to estradiol levels in trials of androgen replacement in men. In other words, hormonal optimization is still in its infancy.

7. **Drugs**

i. There will likely be gaps between the most optimal (desired) state and what can be achieved through the interventions above. By first fixing the systems above—generally in the order they are presented—one can at least identify the minimum effective dose of a drug to bridge the gap;

ii. Because drugs have at least two types of effects—intended (and generally positive) and unintended (and often, but not always, negative)—I can't emphasize enough the need to find the minimum effective dose;

iii. The spectrum of where pharmacologic intervention comes into play is vast, but my view is that some of the more common interventions where risk is outweighed by benefit include additional risk reduction for CHD and CVD (e.g., apoB reduction via drugs that target sterol synthesis and/or absorption); mood stabilization (e.g., the use of low doses of lithium); and increasing insulin sensitization (e.g., the use of AMP kinase activators);

iv. Perhaps, one day, we will add mTOR inhibitors, such as rapamycin or its derivatives, to this list.

8. **Avoid stupid things**

i. Don't smoke

ii. Always wear a seat belt

iii. Never drink and drive

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iv. Never text and drive

v. Situational awareness

vi. Etc…

While I do not believe there is any magic pill on the horizon to stop time indefinitely, I do believe many options exist today—especially when combined with robust metabolic and genetic testing—to achieve our maximum genetic longevity and performance optimization. It is, therefore, my conviction that a highly focused, and relatively early, intervention to course-correct the inevitable can offer our best shot at longevity and optimal performance.

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